REMARKS

Claims 136-152 and 155 are pending and under examination in the subject application. No claim has been added, canceled, or amended herein. Accordingly, claims 136-152 and 155 are still pending and under examination.

In view of the arguments set forth below, applicants maintain that the grounds of the Examiner's rejections made in the August 24, 2005 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw these grounds of rejection.

The Claimed Invention

This invention provides methods of diagnosing a thyroid condition in a subject. One method, that of claims 136-141 and 155 (as dependent thereon) comprises obtaining a suitable unconcentrated urine sample from the subject, and determining a concentration of thyroid stimulating hormone (TSH) in the sample by a method which is not a radioimmunoassay, wherein (i) a concentration of TSH greater than about 0.35 μIU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, diagnoses hypothyroidism in the subject, and (ii) a concentration of TSH less than about 0.04 μIU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, diagnoses hyperthyroidism in the subject.

Another method, that of claims 142-152 and 155 (as dependent thereon), comprises obtaining a suitable unconcentrated urine sample from the subject, and

determining a concentration of TSH and a concentration of thyroxine in the sample by a method which is not a radioimmunoassay, wherein (i) a concentration of TSH greater than about 0.35 μIU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, and a concentration of thyroxine greater than about 1.5 ng/ml in the subject's urine diagnoses hypothyroidism in the subject, and (ii) a concentration of TSH less than about 0.04 μIU/ml in the subject's urine, as determined using the WHO reference standard WO 80/558, and a concentration of thyroxine less than about 0.3 ng/ml in the subject's urine diagnoses hyperthyroidism in the subject.

This invention is based on applicants' *surprising* discovery that measuring the concentration of either (1) *urinary TSH* or (2) *urinary TSH and urinary thyroxine* can *reliably* detect hypothyroidism and hyperthyroidism. In addition, this invention is characterized by the use of a urine sample which is *unconcentrated*.

Rejection Under 35 U.S.C. §103(a) - Obviousness

The Examiner rejected claims 136-141 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuku, et al. (Journal of Endocrinology, 1974, Vol. 62, pages 645-655), in view of Schuurs, et al. (U.S. Patent No. 4,016,043).

In response to the Examiner's rejection, applicants respectfully traverse. Applicants maintain that the Examiner has failed to make a *prima facie* case of obviousness.

The claimed invention is discussed above.

For *prima facie* obviousness to exist, the cited references in combination must (i) teach all elements of the claimed invention, (ii) create a motive to combine, and (iii) create a reasonable expectation of success. The cited references fail to do this.

Specifically, the references, when combined, do not teach all elements of the claimed method. For example, neither reference teaches the element of an *unconcentrated urine sample* recited in the claims, as amended. The Examiner asserts that using unconcentrated urine would be an obvious variation as purification steps would thereby be eliminated. However, applicants maintain that the Examiner's assertion is based on hindsight, and does not factor in applicants' surprising discovery that measuring the concentration of either (1) urinary TSH or (2) urinary TSH and urinary thyroxine can reliably detect hypothyroidism and hyperthyroidism.

Thus, Kuku, et al. and Schuurs, et al., in combination, fail to teach or suggest all elements of the claimed invention. It follows that these references also fail to provide a motive to combine as a reasonable expectation of success.

Furthermore, applicants traverse the Examiner's position that Kuku et al. teach the TSH concentration ranges of the claims, and maintain as flawed the Examiner's method of comparing the claimed invention with the teachings of Kuku, et al. In short, the claimed invention comprises

measuring the *concentration* of TSH, i.e., the amount of TSH per unit volume of fluid at a single time point. Kuku et al., in contrast, teach measuring the *rate* of urinary excretion of TSH, i.e., the amount of TSH secreted per unit of time. These two notions are entirely distinct, despite certain quantitative relationships between them which might exist under certain circumstances. To equate them as the Examiner has done is flawed.

The Examiner also rejected claims 142-152 and 155 under 35 U.S.C. §103(a) as allegedly unpatentable over Kuku et al., in view of Schuurs, et al. and Philo, et al. (U.S. Patent No. 5,108,896).

In response to the Examiner's rejection, applicants respectfully traverse.

The claimed invention is discussed above, as is the standard for a *prima facie* case of obviousness.

Kuku et al. and Schuurs, et al. combined fail to teach all elements of the method of claims 142-152 and 155, for the reasons set forth above regarding claims 136-141. Philo, et al., combined with these two references, fails to cure their shortcomings, in that Philo, et al. fail to teach or suggest (i) the element of an unconcentrated urine sample recited in the claims, as amended, or (ii) applicants' surprising finding that measuring the concentration of either (1) urinary TSH or (2) urinary TSH and urinary thyroxine can reliably detect hypothyroidism and hyperthyroidism. Instead, Philo, et

al. provide a general teaching of simultaneous immunoassays of two analytes using dual enzyme-labeled antibodies.

Thus, Kuku, et al., Schuurs, et al. and Philo, et al., in combination, fail to teach or suggest all elements of the claimed invention. It follows that these references also fail to provide a motive to combine or a reasonable expectation of success.

In view of the above, applicants maintain that claims 136-152 and 155 satisfy the requirements of 35 U.S.C. §103.

Third Supplemental Information Disclosure Statement

Applicants are filing this third supplemental Information Disclosure Statement to supplement the Information Disclosure Statement filed on February 19, 2002, the supplemental Information Disclosure Statement filed on March 5, 2003, and the second supplemental Information Disclosure Statement filed on July 13, 2005 in connection with the subject application.

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and pursuant to 37 C.F.R. §1.97(b)(4), applicants direct the Examiner's attention to the references which are listed on the attached Form PTO-1449 **(Exhibit A)**. Copies of references 2-9 are attached hereto as **Exhibits 1-8**, respectively.

1. U.S. Patent No. 4,332,784 A, issued June 1, 1982 to

The Radiochemical Centre Ltd.;

2. European Patent Application No. 92204048.0, filed December 22, 1992, European Publication No. EP 0 550 108 A1, published July 7, 1993, on behalf of Akzo N.V. (**Exhibit 1**);

3. Supplementary European Search Report, issued October 10, 2005, in connection with European Patent Application No. 01955988.9, filed July 26, 2001, on behalf of Biodiagnostics, Inc. **(Exhibit 2)**;

4. Habermann, J. et al. (1976) "Simultane radioimmunologische Bestimmung von Thyroxin (T_4) and Trijodthyronin (T_3) im Urin (Simultaneous radioimmunoassay for urinary thyroxine (T4) and triiodothyronine (T3))," *J. Clin. Chem. Clin. Biochem.* 14(12): 595-601 (**Exhibit 3**);

5. Lopresti, J.S. et al. (1991) "Characteristics of 3, 5, 3'-triiodothyronine sulfate metabolism in euthyroid man," *J. Clin. Endocrinol. & Metabolism* 73: 703-709 (**Exhibit 4**);

6. Michalke, B. et al. (1999) "Iodine speciation in biological samples by capillary electrophoresis - inductively coupled plasma mass spectrometry," *Electrophoresis* 20: 2547-2553 (**Exhibit 5**);

7. Baisier, W.V. et al. (2000) "Thyroid insufficiency. Is TSH measurement the only diagnostic tool?," *J. Nutr. & Envir. Med.* 10: 105-113 (**Exhibit 6**);

8. Bianchi, R. et al. (1984) "Comparison of plasma and urinary methods for the direct measurement of the thyroxine to 3, 5, 3'-triiodothyronine conversion rate in man," *J. Clin. Endocrinol. & Metabolism* 58: 993-1002 (**Exhibit 7**); and

9. Wilders-Trusching, M.M. et al. (1993) "The effect of treatment with levothyroxine or iodine on thyroid size and thyroid growth stimulating immunoglobulins in endemic goitre patients," *Clin. Endocrinol.* 39: 281-286 (**Exhibit 8**).

European Patent Application No. 01955988.9 is a foreign counterpart of the subject application. A Supplementary European Search Report was issued on October 10, 2005 in connection with European Patent Application No. 01955988.9. A copy of the Search Report is attached hereto as **Exhibit 2**. Above listed references 1-9 were cited in the Search Report. A copy of references 2-9 are attached hereto as **Exhibits 1-8**, respectively. Applicants note that the remaining references listed in the October 10, 2005 Search Report were previously submitted to the U.S. Patent Office in connection with the subject application.

Pursuant to 37 C.F.R. §1.97(c)(1), no fee is deemed necessary in connection with the filing of this third supplemental Information Disclosure Statement.

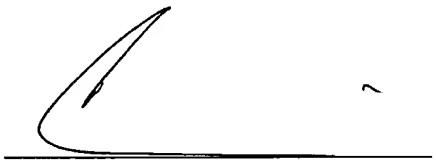
Summary

Applicants maintain that claims 136-152 and 155 are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $620.00 sum, which includes the RCE filing fee and the two-month extension of time fee, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1/24/06
Alan J. Morrison Date
Reg. No. 37,399

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400